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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	8

DATE MAILED: 09/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,887	NEGRIER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 7-11 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 7-11 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 7-11 are pending in the present application, and they are examined on the merits herein.

Drawings

The subject matter of this application admits of illustration by a drawing to facilitate understanding of the invention. Applicant is required to furnish a drawing under 37 CFR 1.81. No new matter may be introduced in the required drawing.

Claim Objections

Claim 7 is objected to because of the following informalities: The phrase "preparing a modified Factor VIII cDNA comprising a deletion of the B-domain and insertion of the truncated Factor IX intron 1" is grammatically incorrect. This is because as written, the modified Factor VIII cDNA contains active steps of deletion and insertion. Should not be these active steps are for the preparation process? The phrase - - preparing a modified Factor VIII cDNA, wherein said preparing comprising a deletion of the B-domain and an insertion of the truncated Factor IX intron 1 - - should obviate this objection. Appropriate correction is required.

Similarly, claim 8 is objected because of the phrase "preparing a modified Factor VIII cDNA comprising a replacement of the B-domain with nucleotides encoding four arginines and insertion of the truncated Factor IX intron 1" for the same reasons discussed above. The phrase - - preparing a modified Factor VIII cDNA, wherein said

preparing comprising a replacement of the B-domain with nucleotides encoding four arginines and insertion of the truncated Factor IX intron 1 - - should obviate this objection.

Priority

Applicants' claim that this application is a divisional application of U.S. Serial No. 09/526,935, now U.S. Patent No.6,271,025, is acknowledged. However, the parent application upon which priority is claimed fails to provide adequate support for claim 11 of this application. Specifically, the concept of introducing splice sites into a wildtype cDNA, then preparing a modified cDNA by inserting one or more introns into these splice-sites has not been taught in the parent application. Applicants are invited to point out specific pages and specific lines in the parent application where such a concept is taught or contemplated. Therefore, claim 11 of the present application is entitled to the priority date of 6/15/01.

Specification

Please check for numerous typographical errors throughout the specification. For examples, "locatons" on line 3 in an abstract paragraph; the phrase "modified amino-acids" in the last line of page 3 refers to modified nucleotides. Additionally, please insert appropriate SEQ ID NOs. to listed nucleotide and amino acid sequences throughout the specification to comply with the sequence rules.

Written D scription

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to a process for producing a protein, said process comprises introducing splice sites into a wild-type cDNA encoding a protein, then inserting one or more introns from one or more additional cDNAs into the wild-type cDNA containing splice sites, followed by introducing into a cell the modified cDNA for the production of the protein wherein the yield of the produced protein with the modified cDNA is greater than the yield produced by the wild-type cDNA. The instant claim encompasses the introduction of any intron, any splice site into any location on any wild-type cDNA encoding a protein, so that upon introducing the modified cDNA into a cell the yield of the protein produced with the modified cDNA is greater than that produced with the wild-type cDNA. Apart from disclosing the insertion and use of a truncated intron I of factor IX having SEQ ID NO:9 into a cDNA encoding a factor VIII

that lacks the B domain at one or more specific sites where factor VIII introns were spliced (e.g., intron I, intron 12, intron 13) resulting in a significant better production of factor VIII in CHO cells and HepG2 cells relative to the unmodified cDNA, the instant specification fails to teach a representative number of introns and/or modified cDNAs having the recited limitations, so that upon introducing a cell the yield of the protein encoded by the modified cDNAs is greater than the yield produced with the unmodified cDNAs. Additionally, the instant specification fails to teach the essential core structural elements possessed or shared by the introns and/or splice sites to confer the modified cDNAs an ability to yield of greater production of the encoded protein in a cell relative to the unmodified cDNAs. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a broad genus of modified cDNA construct encoding a protein to be utilized in the claimed method to attain the desired results (e.g., a greater production of the encoded protein produced by the modified cDNA than the production produced by the unmodified cDNA), and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written

description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte*

Forman, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claim is drawn to a process for producing a protein comprising: a) obtaining a wildtype cDNA of the protein; b) introducing splice sites into the wildtype cDNA; c) preparing a modified cDNA by inserting one or more introns from one or more additional cDNAs into the wildtype cDNA; d) introducing the modified cDNA into a cell; and e) expressing the polypeptide encoded by the modified cDNA in the cell to produce the protein, wherein the yield of the protein produced with modified cDNA is greater than the yield produced with wildtype cDNA.

The instant claim encompasses a process for producing a protein using any cDNA encoding a protein that has been modified by the introduction of any splice sites into the cDNA at any site, and by the insertion of any intron into the cDNA at any site, not necessarily into the splice sites, so that upon introducing the modified cDNA into a cell, the yield of the protein produced with the modified cDNA is greater than the yield produced with the unmodified cDNA. The instant specification is not enabled for such a claimed method. This is because apart from disclosing the insertion of a truncated intron I of factor IX having SEQ ID NO:9 into a cDNA encoding a factor VIII that lacks the B domain at one or more specific sites where factor VIII introns were spliced (e.g., intron I, intron 12, intron 13), and expressing the modified cDNA in CHO cells and HepG2 cells results in a significantly better production of factor VIII relative to the unmodified cDNA, the instant specification fails to offer any guidance for a skilled artisan on the use of any splice sites to be introduced any where in any cDNA encoding

a protein, including a protein whose genomic structure has yet been determined; or any guidance on the source of cDNAs containing any introns where the introns are inserted into the modified cDNA at any site, such that upon introducing the modified cDNA into a cell, the yield of the protein produced with the modified cDNA is greater than the yield produced with the unmodified cDNA. With the lack of sufficient teachings regarding on a representative number of introns and/or modified cDNAs having the recited limitations, as well as any teachings on the essential core structural elements possessed or shared by the introns and/or splice sites, the exact insertion sites for any cDNA encoding a protein, so that the modified cDNAs has an ability to yield of greater production of the encoded protein in a cell relative to the unmodified cDNAs, it would have required undue experimentation for a skilled artisan to make and use the method as claimed. Moreover, the exemplifications show that there is a great variation in the yields of factor VIII produced even using modified cDNAs having a specific truncated intron I of IX of SEQ ID NO:9 into cDNA encoding a factor VIII that lacks the B domain at one or more specific sites where factor VIII introns were spliced (e.g., FVIII I1+13; FVIII I12 and FVIII I1). For example, with the modified cDNA construct of FVIII I12, there is no FVIII protein produced in HepG2 cells (see example 4.2, Fig. 5); the amounts of mRNA and intracellular protein levels for cells transfected with FVIII, FVIII I1 and FVIII I1+12 constructs are very similar and significantly less than those observed for the FVIII I1+13 construct (see Figs. 6 & 7). Furthermore, it is noted this variation in the production of factor VIII was obtained despite the controls for the biosynthesis FVIII at various transcriptional and translational levels have been well characterized in the art, let alone

for the desired enhanced production of any protein using any modified cDNA containing any introns and any splice sites being inserted at any site within the modified cDNA. With the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

Furthermore, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the method as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 11, the phrase "inserting one or more introns from one or more additional cDNAs into the wildtype cDNA" is unclear. Normally cDNAs do not contain introns, so which introns from which additional cDNAs? Additionally which wildtype cDNA? Is it the wildtype cDNA of step a) or the wildtype cDNA containing splice site of step b)? If it is the wild type cDNA of step a), then what is the relationship or nexus of step b) with other steps within the claimed method? The metes and bounds of the claims are not clearly determined.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,271,025. Although the conflicting claims are not identical, they are not patentably distinct from each other because the modified Factor VIII cDNAs in the issued U.S.

Patent having the same structural elements as those of the present application are also taught for producing Factor VIII protein in a cell.

Examiner noted that the claims of the instant specification were not restricted in the parent application with the Serial No. 09/526,935, now U.S. Patent No. 6,271,025.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

DAVE T. NGUYEN
PRIMARY EXAMINER